United States Court of Appeals for the Federal Circuit

ALLERGAN, INC., AND DUKE UNIVERSITY,
Plaintiffs-Appellees,

v.

APOTEX INC., APOTEX CORP., SANDOZ, INC., AND HI-TECH PHARMACAL CO., INC.,
Defendants-Appellants.

2013-1245, -1246, -1247

Appeals from the United States District Court for the Middle District of North Carolina in Nos. 10-CV-0681, 11-CV-0298, and 11-CV-0650, Judge Catherine C. Eagles.

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ALLERGAN, INC., AND DUKE UNIVERSITY,
Plaintiffs-Appellees,

v.

WATSON PHARMACEUTICALS, INC., now known as Actavis, Inc., WATSON LABORATORIES, INC., AND WATSON PHARMA, INC.,
Defendants-Appellants.

2013-1249

Appeal from the United States District Court for the Middle District of North Carolina in No. 12-CV-0321, Judge Catherine C. Eagles.

Decided: June 10, 2014

JONATHAN E. SINGER, Fish & Richardson P.C., of Minneapolis, Minnesota, argued for plaintiffs-appellees. With him on the brief were DEANNA J. REICHEL; and JUANITA R. BROOKS, of San Diego, California. Of counsel was JEFFREY T. THOMAS, Gibson, Dunn & Crutcher, LLP, of Irvine, California.

DEANNE M. MAZZOCHI, Rakoczy Molino Mazzochi Siwik LLP, of Chicago, Illinois, argued for defendants-appellants Apotex Inc., et al. With her on the brief were WILLIAM A. RAKOCZY, PAUL J. MOLINO, and ANDREW M. ALUL, for Apotex Inc., et al; MEREDITH MARTIN ADDY, THOMAS FILARSKI, and BRANDON C. HELMS, Steptoe & Johnson LLP, of Chicago, Illinois, for Sandoz Inc.; STEVEN ROTH, Hi-Tech Pharmacal Co., Inc., of Amityville, New York, and THOMAS J. VETTER, Lucas & Mercanti, LLP, of New York, New York, for Hi-Tech Pharmacal Co., Inc.; and GARY E. HOOD, ROBYN H. AST and MARK T. DEMING, Polsinelli PC, of Chicago, Illinois for Watson Pharmaceuticals, Inc., et al. Of counsel were LUKE T. SHANNON and HARVEN V. DESHIELD, Locke Lord LLP, of Chicago, Illinois, for Apotex Inc., et al.

Before PROST,* C*hief Judge*, REYNA and CHEN, *Circuit Judges.*

Opinion for the court filed by *Chief Judge* PROST. Opinion dissenting in part filed by *Circuit Judge* CHEN.

PROST, *Chief Judge*.

Apotex Inc., Apotex Corp., Sandoz, Inc., Hit-Tech Pharmacal Co., Inc., Actavis, Inc., Watson Laboratories, Inc., and Watson Pharma, Inc. (collectively "appellants") appeal from a final judgment of the U.S. District Court for the Middle District of North Carolina finding that appellants had infringed claims of U.S. Patent Nos. 7,388,029 ("'029 patent") and 7,351,404 ("'404 patent") and had failed to establish they were invalid. For the reasons stated below, we reverse the district court's findings with respect to the validity of each patent.

BACKGROUND

Plaintiff-appellee Allergan, Inc. ("Allergan") has U.S. Food and Drug Administration (FDA) approval to sell Latisse®, a 0.03% bimatoprost ophthalmic solution, as a topical solution to treat hypotrichosis (i.e., hair loss or reduction) of the eyelashes by stimulating hair growth.

Bimatoprost is a synthetic prostaglandin F-2-alpha ("PGF") analog. Prostaglandins are naturally occurring molecules that bind to receptors on the surface of cells. When prostaglandins bind to a cell's receptors, they generate signals that change the way that the cell functions, for example, by controlling cell growth. Because of the ability of prostaglandins to control cell properties, they are significant targets for pharmaceutical research in a variety of areas. PGF is a particular type of prostaglandin that binds with the FP receptor.

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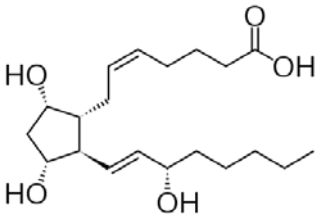
* Sharon Prost assumed the position of Chief Judge on May 31, 2014.

The chemical structure of naturally occurring PGF is illustrated below:



The structure includes a "cyclopentane ring" of carbon atoms, which is illustrated above as the pentagonal structure at the left of the diagram. Two chains of atoms are attached to the ring. The top chain is called the "alpha chain," and the chain below it is called the "omega chain."

By the mid-1980s, it was established that naturally occurring PGF could alleviate intraocular pressure (IOP), which is associated with the eye disease glaucoma. To develop an effective treatment and minimize side effects, scientists worked on synthesizing and testing more selective derivatives and analogs of PGF. A particular kind of PGF analog, 17-phenyl PGF analogs, proved to be particularly useful in the treatment of glaucoma. Bimatoprost is one such synthetic 17-phenyl PGF analog, which emerged in the course of research by Allergan scientists. In 2001, Allergan received FDA approval to sell Lumigan®, a 0.03% bimatoprost ophthalmic solution—identical to Latisse®—as an eyedrop to treat glaucoma, which it continues to market.

Hair loss treatment was another area in which certain PGF analogs proved useful. In the 1990s, Dr. Murray Johnstone performed studies on latanoprost, another kind of 17-phenyl analog. Latanoprost optical solution also received FDA approval for use in glaucoma treatment, and it continues to be marketed as Xalatan®. Dr. Johnstone observed that in the course of treating glaucoma patients with latanoprost eyedrops, a substantial fraction

of them grew much longer and denser eyelash hair. Dr. Johnstone filed a patent application on the use of latanoprost and other 17-phenyl PGF analogs to promote hair growth in February 1997.

The work that led to the '029 patent, the first of the two patents asserted by appellees in this case, was conducted by researchers at Proctor & Gamble led by Dr. Mitchell DeLong. Dr. DeLong and his team studied the effects of a wide range of prostaglandin compounds in mice. In the course of their studies they observed that administration of PGF compounds that were selective for the FP receptor resulted in growth of longer and thicker hair. On March 21, 2000, Dr. DeLong and others filed a provisional patent application on the topical application of compounds that bind the FP receptors to treat hair loss. The '029 patent claims priority to this provisional application. During prosecution, in 2003, the parent application of the '029 patent was assigned to Duke University, and the patent issued on June 17, 2008.

The second patent asserted by appellees in this suit is the '404 patent, which is assigned to Allergan. The '404 patent arises from observations made during the clinical trials for Lumigan®. As had been observed for latanoprost, glaucoma patients treated with bimatoprost eyedrops spontaneously grew longer and thicker eyelash hair. *See* '404 patent col. 11 ll. 5-62. The '404 patent covers the treatment of eyelash hair loss through topical application of bimatoprost, and it claims priority to a provisional application filed on February 4, 2002.

Allergan and Duke University (collectively "appellees") sued each of the appellants under 35 U.S.C. § 271(e)(2)(A) after they submitted Abbreviated New Drug Applications (ANDAs) to the FDA seeking to market a generic version of Allergan's Latisse® product. Appellees asserted claims 1, 8, 14, 18, and 20 of the '029 patent and claim 14 of the '404 patent. After a bench trial in the

consolidated Hatch-Waxman action, the district court held, inter alia, that the asserted claims of the '029 and '404 patents are not invalid for anticipation, obviousness, insufficient written description, or lack of enablement, and, moreover, that appellants infringed. *Allergan, Inc. v. Apotex, Inc.*, Nos. 1:10-CV-681, 1:11-CV-298, 1:11-CV-650, 2013 WL 286251, at *1 (M.D.N.C. Jan. 24, 2013). The district court subsequently enjoined appellants, along with any persons or entities who are in privity with appellants or to whom appellants transfer the ANDA, from commercial manufacture, use, offer to sell and/or sale of the proposed products until the latest of the expiration dates of the '029 and '404 patents. *Allergan, Inc. v. Apotex, Inc.*, No. 1:10-CV-681 Permanent Inj. and Final J. 2-3, ECF No. 231.

This appeal followed, in which appellees raise issues of claim construction for the '029 patent, as well as the invalidity of the asserted claims of the '029 and '404 patents. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

DISCUSSION

I. CLAIM CONSTRUCTION

Claim construction is an issue of law that we review de novo. *Lighting Ballast Control LLC v. Philips Elecs. N. Am. Corp.*, 744 F.3d. 1272, 1276-77, (Fed. Cir.) (en banc); *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454-55 (Fed. Cir. 1998) (en banc). In construing a claim term, we look at the term's plain and ordinary meaning as understood by a person of ordinary skill in the art. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). There is an exception to this general rule when a patentee sets out a definition and acts as her own lexicographer. *Thorner v. Sony Computer Entm't Am., LLC*, 669 F.3d 1362, 1365 (Fed. Cir. 2012).

Appellants raise a single claim construction issue on appeal concerning the '029 patent. The '029 patent's asserted claims are directed towards a method of "treating hair loss." Appellants challenge the district court's construction of this term as "'arresting hair loss, reversing hair loss, or both and promoting hair growth' meaning that the invention may arrest hair loss, reverse hair loss, or promote hair growth in the alternative." All parties, as well as the district court, agreed that the specification provides an express definition for the term: "'Treating hair loss' includes arresting hair loss or reversing hair loss, or both, and promoting hair growth." '029 patent col. 3 ll. 29-30. Appellants argue, however, that use of the conjunctive "and" in the inventor's own lexicography expressly provides that the method for treating hair loss must *both* arrest or reverse hair loss, as well as *also* promote hair growth. Appellants argue that under their proposed construction, a generic version of Latisse® would not infringe because Latisse® treats hair loss by lengthening, thickening, and darkening existing healthy hair—which appellants argue means only the promotion of hair growth.

The district court agreed with the appellees that the use of the word "includes" in the definition of "treating hair loss" plainly means that the patentee intended to define treating hair loss to include the possibility of one or all of arresting hair loss, reversing hair loss, or promoting hair growth. Appellees argue that this comports with the plain meaning of "treating hair loss," which would be understood in the art as including treatments that exclusively promote hair growth. Most compellingly, even if there may be some ambiguity in how the patentee defined the term, numerous examples in the patent describe the use of claimed compositions to "induce hair growth," "darken and thicken eyelashes," "promote hair growth," and "promote eyelash growth." *See, e.g.*, '029 patent at cols. 58 ll. 17-19, 59 ll. 43-44, 59 ll. 61-62, 60 ll. 31-32, 60

ll. 11-12. There is nothing in either the specification or the claims suggesting that the patentee would have excluded these examples from the scope of claimed methods.

Reading the patentee's own lexicography in light of the whole specification, we conclude that a method of "treating hair loss" may include a method of promoting hair growth without also arresting or reversing hair loss. Accordingly, we affirm the district court's construction.

II. INVALIDITY

A. '029 Patent

1. Anticipation

A patent is invalid for anticipation under 35 U.S.C. § 102[1] if a single prior art reference discloses each and every limitation of the claimed invention. *Schering Corp. v. Geneva Pharm.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). A single prior art reference may anticipate without disclosing a feature of the claimed invention if such feature is necessarily present, or inherent, in that reference. *Id.* Anticipation is a question of fact that we review for clear error. *Atlas Powder Co. v. Ireco, Inc.*, 190 F.3d 1342, 1346 (Fed. Cir. 1999).

The presumption of a patent's validity under 35 U.S.C. § 282 can be rebutted by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship,* 131 S.Ct. 2238, 2245-46 (2011). The standard of proof does not "rise and fall with the facts of each case." *Id.* at 2250. In particular, "[w]hether a reference was previously consid-

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[1] The America Invents Act ("AIA"), Pub. L. No. 112–29, took effect on September 16, 2012. Because the applications for the patents at issue in this case were filed before that date, we refer to the pre-AIA versions of §§ 102 and 103.

ered by the PTO, the burden of proof is the same: clear and convincing evidence of invalidity." *Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259-61 (Fed. Cir. 2012).

With respect to the '029 patent, appellants raise two allegedly anticipatory references: (i) the published patent application arising from Dr. Johnstone's aforementioned research on promoting hair growth using latanoprost and related compounds, and (ii) Allergan's earlier patent on the use of bimatoprost and related compounds to treat glaucoma. We discuss each reference in turn.

a. Johnstone PCT Application

Dr. Johnstone's research led to the filing of International Patent Application No. PCT/US98/02289 ("Johnstone") on February 3, 1998. In particular, Johnstone discloses methods for stimulating hair growth using a broad genus of prostaglandin analogs that, among other properties, have an alpha chain with the following structure (*see* Johnstone at 16 ll. 16-22):

The cited art of the '029 patent includes U.S. Patent No. 6,262,105 to Johnstone, which shares its disclosure with the Johnstone PCT application. The Johnstone PCT application was also raised during the prosecution of the '029 patent. Following issue of the initial notice of allowance, the patentee filed an amendment to add a proviso to independent claims with the aim of expressly excluding the compounds disclosed in Johnstone. J.A. 4130-37. The examiner accepted the amendment and issued a notice of allowance for the patent with the claims amended to include the provisos.

Appellants argue that Johnstone anticipates nevertheless. As illustrated above, Johnstone expressly discloses PGF structures in which the alpha chain includes a

double (also known as "unsaturated") bond at the C5-C6 position, shown as a doubled line in the above diagram. The provisos within the '029 claim expressly exclude such a structure. Appellants contend that even so, Johnstone goes on to also disclose compounds with a single (also known as "saturated") bond at the C5-C6 position: "The chain could preferably be a C_6-C_{10} chain which can be *saturated or unsaturated*, having one or more double bonds, and allenes, or a triple bond." Johnstone at 12 ll. 22-24 (emphasis added). As a result of this additional disclosure, in appellants' view, Johnstone also teaches a single, or saturated, bond at the C5-C6 position, which would not be excluded by the provisos and consequently reads on the independent claims of the '029 patent.

Johnstone, however, contains no other disclosure of a structure with a single, saturated, bond at that location. All of the examples of Johnstone are drawn to compositions in which the C5-C6 bond is a double bond. The district court moreover agreed with appellees and found that in the context of the state of the art, a person of ordinary skill would not read Johnstone as disclosing a single bond structure. The district court accepted appellees' evidence that a PGF analog with such a structure would not have been thought to have a therapeutic effect because it would not selectively bind to the FP receptor. *Allergan*, 2013 WL 286251, at *5. The district court further supported its determination by citing to the '029 patent's notice of allowance, in which the examiner indicated Johnstone "lacks motivation to modify the prostaglandins taught therein in order to obtain the presently claimed prostaglandins." *Id.*; J.A. 5559-65 at 5564. The district court found, therefore, that the disclosure on which appellants rely does not "clearly and unequivocally disclose" the use of compounds with the saturated bond. *Allergan*, 2013 WL 286251, at *6 (citing *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1371 (Fed. Cir. 2008)).

We are persuaded that in light of the very limited disclosure, the court did not commit clear error. Appellants are correct that where a disclosure was written to provide an optional ingredient, structure, or step, we have held that the optional component still anticipates. *See Upsher-Smith Labs., Inc. v. Pamlab, L.L.C.*, 412 F.3d 1319, 1320-21 (Fed. Cir. 2005) ("[A] prior art composition that 'optionally includes' an ingredient anticipates a claim for the same composition that expressly excludes that ingredient."); *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001) ("[A]nticipation does not require actual performance of suggestions in the disclosure."). Indeed, even if the reference discloses the option within the context of a reference that "disparages" or "teaches away," we do not consider those issues in the context of an anticipation analysis. *Upsher-Smith*, 412 F.3d at 1323.

The court was not clearly erroneous, however, in its determination that in this case, the disclosure was too sparse and ambiguous for a person of ordinary skill to comprehend Johnstone's disclosure as anticipating the '029 patent. *Net MoneyIN,* 545 F.3d at 1371. Accordingly, we affirm.

b. '819 Patent

U.S. Patent No. 5,688,819 ("'819 patent") emerged from research by Allergan scientists on selective PGF analogs that could effectively treat glaucoma. The '819 patent discloses the use of a set of selective PGF analogs, including bimatoprost, which is specifically identified by its chemical structure. '819 patent col. 7 ll. 44-46. The '819 patent does not refer to hair growth or treating hair loss, nor does it disclose topical application of any compounds. Appellants argue, however, that because (i) the '819 patent's disclosure teaches the application of eyedrops containing compounds within the scope of the asserted '029 patent claims, in particular bimatoprost,

and (ii) the application of eyedrops containing bimatoprost results in the growth of eyelashes, the disclosed method inherently anticipates the '029 patent.

At issue is whether promoting hair growth through topical application of bimatoprost on the skin is necessarily present or inherent in the method of applying eyedrops containing bimatoprost.[2] *Schering*, 339 F.3d at 1377. There is no dispute that the application of eyedrops containing bimatoprost *can* result in the promotion of eyelash hair. Allergan's own description of the conception of the '404 patent was that scientists first observed that after monkeys were treated with bimatoprost in their eyes, some of them showed enhanced eyelash growth. Appellees' Br. 13 (citing J.A. 396-98, 5617-29, 5624). Similar results were found in clinical trials, during which some patients who used bimatoprost eyedrops reported eyelash growth. *Id.* at 15 (citing J.A. 525-33, 5855-71).

The '404 patent, moreover, includes as its enabling example the administration of bimatoprost by eyedrop in a study of patients. '404 patent col. 10 l. 38-col. 12 l. 3. As such, the specification recites a direct link between eyedrop administration and the claims directed to topical application: "the course of treatment with eye drops" results in excess fluid gathering in the lid area, which in turn once wiped gets to "the adjacent skin of the lid area." *Id.* at col. 10 ll. 51-56. Appellants argue that if the '819 patent discloses a method of eyedrop administration of

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[2] Not all asserted claims of the '029 patent are limited to topical application, and irrespective of the answer to this more narrow question, those claims may be inherently anticipated by the '819 patent's disclosure of systemic administration. Appellants do not raise this issue, and in any event, appellees assert claim 14, which is so limited.

bimatoprost that is sufficient to enable the claims of the '404 patent, then that method must also inherently anticipate.

The district court rejected appellants' arguments. The district court found that appellees' expert witness, Dr. Noecker, had persuasively testified that a "properly applied drop" would not transfer to the skin. *Allergan*, 2013 WL 286251, at *6. The district court additionally found that Lumigan® clinical trials only showed that a fraction of patients experience eyelash growth. *Id.* The district court found that because a bimatoprost eyedrop only *may* contact skin, the '819 patent does not inherently anticipate as inherency "may not be established by probabilities or possibilities." *Id.* (citing *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011).

Appellants argue that the district court erroneously required *certainty* as a prerequisite for inherent anticipation. In their view, the district court should not have relied on the finding that only some patients who received eyedrops experienced eyelash growth.

Appellants are correct that inherent anticipation can be found based on a trace amount. For example, we have held that a chemical process that produces only "trace" amounts of a compound inherently anticipates that compound. *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1344 (Fed. Cir. 2005). All that needs to be shown is that the outcome of the process be a "natural result flowing from the operation as taught in the prior art." *Id.* (citing *In re Oelrich*, 666 F.2d 578, 581 (CCPA 1981)). We have also held that a product would be inherently anticipated where it was a natural result of the prior art process, even when it would be possible to prevent the formation of the product through "extraordinary measures." *Atlas Powder*, 190 F.3d at 1349.

We review the district court's findings of fact on inherent anticipation for clear error. In this case, the

district court found that it was at least *possible* to administer eyedrops in a way as to reduce the flow of liquid to the eye to close to zero. *Cf. Glaxo Inc. v. Novopharm Ltd.*, 52 F.3d 1043, 1047 (Fed. Cir. 1995). The district court also found no express teaching in the '819 patent that described how fluid from the eyedrop could transfer to the skin. *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999). We cannot say either of these findings, nor the conclusion that the prior art does not necessarily include the claimed limitations, is clearly erroneous. Accordingly, we are not persuaded that the district court committed clear error in finding that the '819 patent does not inherently anticipate the claims of the '029 patent, and we affirm.[3]

2. Obviousness

Appellants alternatively allege that the aforementioned references render obvious the asserted claims of the '029 patent. A patent is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Obviousness is a legal conclusion based on underlying facts. *Graham v. John Deere Co.,* 383 U.S. 1, 17 (1966).

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[3] Appellants raise the same arguments regarding inherent anticipation of the asserted claim of the '404 patent, which similarly claims the topical application of bimatoprost specifically as a method of promoting eyelash growth. We affirm the district court's finding of no inherent anticipation of the '404 patent on the same grounds as explained for the '029 patent.

On appeal from a bench trial, we review the underlying findings of fact for clear error, and we review de novo the court's ultimate legal conclusion of whether the claimed invention would have been obvious. *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1354 (Fed. Cir. 2013). Underlying factual inquiries include (i) the scope and content of the prior art; (ii) the differences between the prior art and the claims at issue; (iii) the level of ordinary skill in the field of the invention; and (iv) relevant secondary considerations including commercial success, long-felt but unsolved needs, failure of others, and unexpected results. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007); *Graham*, 383 U.S. at 17-18.

The district court held that the '029 patent was nonobvious, based principally on its finding that there was no motivation to combine Johnstone and the '819 patent due to "pharmacological differences" between the compounds that each reference discloses. *Allergan*, 2013 WL 286251, at *9. Specifically, the '819 patent discloses a list of thirteen chemical compositions for 17-phenyl PGF analogs, which were like those disclosed in Johnstone in that they contain a C5-C6 double bond and have demonstrably high pharmaceutical activity in treating intraocular pressure with minimal side effects. '819 patent col. 3 ll. 9-18, col. 7 ll. 19-57. However, the '819 patent's compounds contain a C1-amide group whereas Johnstone generally discloses compounds with esters or carboxylic acids at the C1 location. The district court was persuaded by Allergan's expert that it was understood at the time of the invention of the '029 patent that because of this C1-amide group, bimatoprost and the other 17-phenyl PGF analog compositions disclosed in the '819 patent were thought to bind to a receptor other than the FP receptor.

As a result, even though the '819 patent compounds were like the Johnstone compounds in that they were 17-phenyl PGF analogs that had proved effective in treating

glaucoma, the district court agreed that a person of ordinary skill would not have been motivated to use any C1-amide compounds to treat hair loss. The district court found that such "pharmacological differences are especially significant in the hair growth field," as "hair growth is and was unpredictable and mysterious," pointing to data that showed that certain glaucoma drugs based on prostaglandin analogs only result in low levels of eyelash growth. *Allergan*, 2013 WL 286251, at *10. The district court determined that secondary considerations additionally weighed in favor of non-obviousness, based on its finding that the invention of the '029 patent was an unexpected result (for the same reasons that it found a lack of reasonable expectation of success), as well as the commercial success of Latisse® and the paucity of competing hair growth treatments.

The district court reached its conclusion of nonobviousness by looking only at properties of the C1-amide group and, particularly, bimatoprost. In doing so, the district court erred by failing to take into account the full scope of the '029 patent claims.[4] "[T]he person of ordinary

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[4] The record before us does not demonstrate that the appellants' obviousness arguments regarding the '029 patent were limited to the obviousness of bimatoprost. Rather, it appears the district court failed to account for the full scope of the '029 patent claims despite appellants' raising such an assertion in its pre- trial brief, post-trial brief, and proposed findings of fact. *See* Letter from Appellants, Ex. A (Excerpt of Defendants' Amended Proposed Findings of Fact and Conclusions of Law) 6-7, 11-12, ECF No. 94 (contending that the asserted claims of the '029 patent are obvious over Johnstone alone in view of the knowledge of those of ordinary skill in the art); *see also Allergan, Inc. v. Apotex, Inc.*, No. 1:10-CV-681 Defs.' Opening Post-Trial Br. 47-48, ECF No. 190 (arguing that

skill need only have a reasonable expectation of success of developing the *claimed invention*." *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013) (emphasis added). The '029 patent is not limited to compounds with a C1-amide group, such as bimatoprost or the broader class of compounds described in the '819 patent. The scope of the independent claims of the '029 patent encompasses thousands of permutations of PGF analogs, including structures with all kinds of functional groups at the C1 location, such as carboxylic acids, alkyl carboxylates, and hydroxyls.[5] Given the breadth of the '029 patent's claimed invention, appellants did not have the exacting burden of showing a reasonable expectation of success in using the narrow class of PGF analogs with C1-amide groups to treat hair loss, let alone a reasonable expectation of success in using bimatoprost *in particular*. Appellants instead had the burden of showing that any compounds within the broad genus claimed by the '029 patent, including those that did not have C1-amide groups, were obvious at the time of the invention.

The district court's reasoning was especially problematic because the feature of bimatoprost that it relied on

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plaintiffs did not show a nexus to unexpected results and other secondary considerations within the scope of the '029 claims).

[5] For example, claim 1 of '029 patent, which describes the functional group at the C1 location as "R^1," recites that it claims structures "wherein R^1 is selected from the group consisting of C(O)OH, C(O)NHOH, $C(O)OR^3$, CH_2OH, $S(O)_2R^3$, $C(O)NHR^3$, $C(O)NHS(O)_2R^4$, tetrazole, a cationic salt moiety, a pharmaceutically acceptable amine or ester comprising 2 to 13 carbon atoms, and a biometabolizable amine or ester comprising 2 to 13 atoms."

was that it and the other PGF analogs with a C1-amide group disclosed in the '819 patent bind to a variant of the FP receptor.[6] Neither the district court nor appellees explain the nexus between this finding and the broad scope of '029 patent's claimed invention. The '029 patent's claimed invention is not unique to PGF analogs that bind the variant FP receptor. The '029 patent also claims compounds that do bind the garden-variety FP receptor, such as C1-esters and C1-carboxylic acids. Indeed, almost every disclosed exemplar in the '029 patent describes one of the latter compounds. The district court's improperly limited analysis meant that it did not answer the question prerequisite to its conclusion. The district court needed to have found that other embodiments falling within the claim will behave in the "same manner" as compounds with C1-amide groups, in order to establish that evidence of unexpected results "is commensurate with the scope of the claims."[7] *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). The district court failed, however, to make a finding on how the C1-amide compounds' property of binding to the *variant* FP receptor necessarily applied to the reasonable expectation of success for the full scope '029 patent's claimed invention, which included the

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[6] Appellees take the position, which appellants dispute, that bimatoprost interacts with a splice variant of the FP receptor, i.e., a form of the FP receptor in which the sub-units of the structure receptor have been rearranged. *See* Appellees' Br. 19, n.2.

[7] This is in contrast with circumstances such as those in *Genetics Institute, LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1308-09 (Fed. Cir. 2011). There, the court noted that unexpected results applied across the full scope of a claimed protein structure, since any exceptions were limited to minor variations within only "10%" of the claimed structure.

utility of compounds that bound the normal FP receptor to treat hair loss.

The district court compounded its error by taking an overly cramped view of what the prior art teaches. The person of ordinary skill reading Johnstone would have found it replete with references to the advantages of using 17-phenyl PGF compounds generally, including those with carboxylic acids, esters, and other related groups at the C1 location—all covered by the '029 patent's claims. We do agree with the district court that Johnstone does not "clearly and unequivocally disclose" compounds that also include a C5-C6 saturated bond to the extent that it would *anticipate* the '029 patent, as explained above in section II.A.1.a. This does not diminish, however, the fact that Johnstone *does* suggest the possibility of using a PGF analog structure that would include such a bond, merely without adequate explanation within the reference itself. *See* Johnstone at 12 ll. 22-24. A motivation to combine may be implicit in the prior art—silence does not imply teaching away. *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005); *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1291 (Fed. Cir. 2006) (rejecting the necessity of an express disclosure of motivation where it "may be found *implicitly* in the prior art"). Johnstone's mere disclosure of alternative preferences does not teach a person of ordinary skill away from the broad swath of compounds within the scope of the '029 patent. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

Johnstone does not even teach away from compounds that bind variant forms of the FP receptor. On the contrary, Johnstone even provides an alternative preference for the PGF analogs that were known to have different FP receptor binding properties—the vasodilatory compounds taught in the parent of the '819 patent, U.S. Patent No.

5,352,708. Johnstone at 17 ll. 13-15.[8] The conclusion of Johnstone's detailed description makes this clear. What Johnstone unequivocally teaches is that "[p]rostaglandin derivatives that *exhibit high pharmacological activity and no or only very small side effects*, such as [latanoprost] and its carboxylic acid esters, are also presently particularly preferred, especially in use in large areas of the skin and the scalp." *Id.* at 22 ll. 21-23 (emphasis added). Johnstone discloses a preference for PGF analogs that had already been identified and were known in the art to have selective pharmacological activity, irrespective of whether such activity was due to binding to the FP receptor or a variant, as well as whether there was a saturated or unsaturated bond at the C5-C6 location. The dissent inappositely emphasizes the complexity of *changing* a bond at this location, implying that the '029 patent represents compounds that are newly isolated or synthesized over those of Johnstone. Dissenting Op. at 5-6. However, following Johnstone, there was nothing left for a chemist

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[8] To be sure, we agree with appellees (and the dissent, which addresses this issue at length, *see* Dissenting Op. at 7-8) that appellants fail to show that this is a sufficiently clear reference to the '819 patent itself, since the list of compounds expressly disclosed as being vasodilatory in the '708 patent exclude the 17-phenyl PGF analogs that the '819 patent discloses, such as bimatoprost. Rather, the point is that the analogs disclosed in the '708 patent and its progeny, including the '819 patent, had different chemical structures and properties—including, for example, the binding of variant FP receptors. This is especially salient because the district court's conclusion relied so heavily on its finding that—even in light of Johnstone's disclosure—the utility of a compound that binds a variant FP receptor was an unexpected result.

to do. As discussed above, Johnstone taught squarely towards a new utility for a finite set of already identified and isolated compounds with properties that had already been characterized—for example, as disclosed in the '708 and '819 patents.

The district court also did not find any express teaching away in the art as a whole. The district court did find that the prior art included PGF analogs other than those disclosed in Johnstone that had identical physiological effects, as evinced by the '819 patent's disclosure of thirteen such compounds, including bimatoprost, that could be used in reducing intraocular pressure and thereby treating glaucoma. However, the district court concluded that in the context of hair growth as a generally "unpredictable and mysterious" art, *any* difference in the chemical activity of a PGF analog, even one with a structure very similar to one claimed by the '029 patent, would be sufficient to teach away.

But, it does not matter whether hair growth is *generally* an unpredictable endeavor—the question is more narrowly whether the success of using selective PGF analogs to treat hair loss would be reasonably unpredictable. The district court and the dissent commit the same error of examining the state of the art *before* the time of the invention. *See* Dissenting Op. at 9. Once Johnstone was published, the general characteristics of the hair growth art ceased to be relevant. Johnstone taught that PGF analogs could be used to grow hair. Indeed, Johnstone even more specifically taught that PGF analogs that were effective glaucoma drugs could grow hair. Therefore, the correct question, *at the time of the '029 patent's invention*, was whether there was anything "unpredictable and mysterious" about a PGF analog that could treat glaucoma growing hair.

On this point, the district court chiefly cited the failure of certain therapeutic PGF analogs to grow hair—

remarkably, even though eyelash growth was a known potential side effect of one of the two cited examples.[9] Even so, "[o]bviousness does not require absolute predictability of success." *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). What does matter is whether the prior art gives direction as to what parameters are critical and which of many possible choices may be successful. *Id.*; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1366 (Fed. Cir. 2007). Johnstone did not make a general exhortation covering thousands of possibilities—its teaching focused on specific classes of compositions of PGF analogs with specifically described structures and properties that guided persons of ordinary skill in the art to compounds with similar structures that would fall within the scope of the '029 patent's claims. *See Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1007 (Fed. Cir. 2009) ("Obviousness based on structural similarity may be proven by the identification of some motivation that would have led one of ordinary skill in the art to select and modify a known compound in a particular way to achieve the claimed compound."). While success in employing the disclosed compounds to treat hair loss may not have been guaranteed, Johnstone's teaching provided sufficient guidance as to what parameters would lead to a reasonable expectation of success.

The district court's findings on secondary considerations suffer from the same infirmity of lacking a nexus with the scope of the '029 patent's claimed invention. It is the established rule that "objective evidence of nonobviousness must be commensurate in scope with the

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[9] *See Allergan*, 2013 WL 286251, at *10 ("The label for the glaucoma drug Rescula® includes a warning that 10-14% of patients had increased length of eyelashes, 7% had decreased length of eyelashes, and 80% showed no response whatsoever.").

claims which the evidence is offered to support." *Application of Tiffin*, 448 F.2d 791, 792 (CCPA 1971); *see also MeadWestVaco Corp. v. Rexam Beauty & Closures, Inc.*, 731 F.3d 1258, 1264-65 (Fed. Cir. 2013); *In re Huai-Hung Kao*, 639 F.3d at 1068; *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003); *In re Hiniker Co.*, 150 F.3d 1362, 1369 (Fed. Cir. 1998). As discussed above, the district court's findings on unexpected results, which were closely intertwined with its analysis of motivation to combine and reasonable expectation of success, were not commensurate with the full scope of the patent's claims.

In sum, even if the district court did not commit clear error in its findings of fact, failure to consider the appropriate scope of the '029 patent's claimed invention in evaluating the reasonable expectation of success and secondary considerations constitutes a legal error that we review without deference.

Taking an appropriate view of the scope of the '029 patent's claimed invention, the facts found by the district court weigh towards the conclusion of obviousness. The validity of the '029 patent rests on the provisos that exclude certain PGF analog structures from its claim scope, which were designed to avoid anticipation by Johnstone. As discussed above, however, Johnstone contains a plethora of teaching towards PGF analog structures that are outside the scope of the provisos, including an express suggestion to employ compositions with saturated C5-C6 bonds, as well as teaching to PGF analogs that are selective in having maximized therapeutic effect with minimized side effects. The '029 patent claims many different kinds of PGF analog structures, including PGF analogs with both unsaturated and saturated C5-C6 bonds, as well as PGF analogs that both bind the FP receptor and its variant. The district court's finding that bimatoprost and the '819 patent's other disclosed compounds only bind the variant FP receptor is not relevant to the '029 patent's actual claimed invention.

Accordingly, the district court made no finding that would diminish the more probative facts supporting a person of ordinary skill's substantial reasonable expectation of success and motivation to use PGF analogs with high pharmacological activity and structures similar to those disclosed in Johnstone to treat hair loss. Even if we were to determine that the aforementioned flaws in the district court's analysis do not rise to the level of clear error, the evidence of commercial success cannot on its own remedy the district court's other errors leading to its overall conclusion of non-obviousness. [10]

We therefore reverse the district court's finding that the asserted claims of the '029 patent are non-obvious.

B. '404 Patent

1. Brandt References

The '404 patent emerged from the results of Allergan's clinical trials evaluating the safety and efficacy of bimatoprost eyedrops for glaucoma treatment, which were subsequently marketed as Lumigan®. Appellants identify four publications of clinical trials that they allege disclose the ability of bimatoprost to promote eyelash hair growth (collectively the "Brandt references"). Appellants argue that, among other grounds for invalidity, the

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[10] The district court made a further finding that Latisse® was the only drug approved by the FDA and marketed for eyelash hair growth. It further noted that latanoprost, the subject of the Johnstone PCT, has not been approved. It is unclear from the district court's opinion whether this finding related to commercial success or long-felt need. In any event, however, it is undercut by Allergan's exclusive license of the patent that issued from the Johnstone PCT. *See Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005).

Brandt references would render the '404 patent obvious in light of Johnstone. The Brandt references include the following:

> a presentation given by Dr. James Brandt, a clinical investigator working on Lumigan®, to the American Academy of Ophthalmology Meeting on October 23, 2000, disclosing three month results from a bimatoprost eyedrop trial, which identifies the drug only by the name "Lumigan," stating that more than 5% of patients experience eyelash growth;
>
> a press release issued by Allergan on October 23, 2000, containing the same information as the October 23, 2000 presentation;
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> a publication by Drs. Sherwood and Brandt entitled "Six-Month Comparison of Bimatoprost Once-Daily and Twice-Daily with Timolol Twice-Daily in Patients with Elevated Intraocular Pressure" in *Survey of Ophthalmology* in May 2001 disclosing that in a six month glaucoma study, eyelash growth was reported in between 35 and 48% of patients receiving bimatoprost, depending on dose;
>
> a publication by Drs. Brandt, VanDenburgh (a named inventor of the '404 patent), Chen, and Whitcup in *Ophthalmology* in June 2001 disclosing that in a three month study, eyelash growth was reported in between 25.6% and 33.7% of patients receiving bimatoprost, depending on dose.

The first two Brandt references are indisputably prior art under § 102(b), as they were published more than one year before the priority date of the '404 patent, February 4, 2002. These references do not, however, expressly refer to bimatoprost. A person of ordinary skill hence would be unaware that the results reported therein were associated with bimatoprost. With respect to the more fulsome May

and June 2001 references, the district court found that the '404 patent was invented prior to their publication date and, therefore, that the references were not prior art under § 102(a).[11]

a. Date of Invention

The invention date is the date of conception. *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1063 (Fed. Cir. 2005). Conception is "the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." *Burroughs Wellcome Co. v. Barr Labs., Inc.*, 40 F.3d 1223, 1228 (Fed. Cir. 1994). The issue of the conception date of an invention is a legal conclusion based on underlying factual findings. *Taurus IP, LLC v. DaimlerChrysler Corp.*, 726 F.3d 1306, 1322 (Fed. Cir. 2013). While defendants bear the burden of persuasion to show that the Brandt references are prior art to the '404 patent by clear and convincing evidence, the patentee nevertheless must meet its burden of production to demonstrate an earlier conception date. *Mahurkar v. C.R. Bard, Inc.*, 79 F.3d 1572, 1577 (Fed. Cir. 1996).

In evaluating the patentee's evidence of conception date, courts "must give due regard to the trial court's opportunity to judge the witnesses' credibility." Fed. R. Civ. P. 52(a)(6). The court's inquiry is guided by the principle that "[i]t is well established that when a party seeks to prove conception via the oral testimony of a putative inventor, the party must proffer evidence corrob-

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[11] The district court opinion suggests that it found that all four "Brandt references are not prior art under 35 U.S.C. § 102(a)," even though the first two references were published more than one year before the priority date of the '404 patent. *Allergan*, 2013 WL 286251, at *7.

orating that testimony." *Shu-Hui Chen v. Bouchard*, 347 F.3d 1299, 1309 (Fed. Cir. 2003). In particular, the "definite and permanent" idea required for conception "must be supported by corroborating evidence." *Burroughs Wellcome*, 40 F.3d at 1230.

The district court found that the conception date of the '404 patent was in mid-2000 based on the following facts: (i) Dr. Woodward's credible testimony that he reached a "concrete conclusion" that topical application of bimatoprost would grow hair in mid-2000, (ii) Dr. VanDenburgh's credible testimony of meeting with patent attorneys between late 2000 and early 2001 to discuss the invention, and (iii) internal Allergan memoranda reporting eyelash growth in clinical trials, which were received by Drs. Woodward and VanDenburgh in early 2000. *Allergan*, 2013 WL 286251, at *7.

The problem is that to the extent there is any documentary evidence, it does not relate to the claimed invention of the '404 patent—the topical application of bimatoprost for use to promote eyelash hair growth. The Allergan memoranda refer only to eyelash growth resulting from the administration of eyedrops. The memoranda reported the side effects of bimatoprost used in eyedrops and did not disclose the claimed invention of topical application for intended therapeutic effect. The *only* evidence that corroborates Dr. Woodward's testimony that he conceived of *topical application* of bimatoprost in mid-2000 is the oral testimony of his co-inventor, Dr. VanDenburgh. This is not one of the cases cited by appellees in which corroborating evidence is found through multiple written documents, such as a collection of engineering notebooks. *Spansion, Inc. v. Int'l Trade Comm'n*, 629 F.3d 1331, 1356 (Fed. Cir. 2010); *Univ. of Pittsburgh v. Hedrick*, 573 F.3d 1290, 1298 (Fed. Cir. 2009). Rather, this is a case in which there is no corroborating document that shows anything about the claimed invention. The only corroboration of the claimed invention is the oral

testimony of an inventor, which we must treat with skepticism due to the possibility of an inventor's self-interest in obtaining or maintaining an existing patent. *Shu-Hui Chen*, 347 F.3d at 1309; *Price v. Symsek*, 988 F.3d 1187, 1994 (Fed. Cir. 1993).

The district court, therefore, committed clear error in finding corroboration of an earlier priority date in documents that collectively do not include any description of the claimed invention of the '404 patent. As the only other potentially corroborating evidence of conception is the oral testimony of a co-inventor, we reverse the district court's finding that the '404 patent was conceived prior to the date of publication of the May and June 2001 Brandt references.

b. Authorship of the Brandt References

Appellees argue that even if the '404 patent cannot claim an earlier priority date, the later Brandt references are still not § 102(a) art as they represent the work of the inventors themselves. "[O]ne's own work is not prior art under § 102(a) even though it has been disclosed to the public in a manner or form which otherwise would fall under § 102(a)." *In re Katz*, 687 F.2d 450, 454 (CCPA 1982). Appellees claim that the Brandt references are the product of the '404 patent's co-inventor Dr. VanDenburgh's work in designing and directing the Lumigan® clinical trials. Appellees rely predominately on Dr. VanDenburgh's testimony regarding her role in the clinical trials, in which she described her role supervising and managing the work being done by various clinical study locations, including writing internal memoranda and reports. This, appellees contend, amounts to Dr. Brandt and other authors of the Brandt references being a "pair of hands" for the '404 patent's inventors, in particular Dr. VanDenburgh. *Mattor v. Coolegem*, 530 F.2d 1391, 1395 (CCPA 1976).

Appellants argue that, as an initial matter, appellees did not timely raise this issue. To the extent that appellees did argue this point, it appears to have been during closing arguments and post-trial briefing.[12] However, under Fourth Circuit law, appellees may have waived the issue of the Brandt references' authorship by not presenting it in pretrial briefing, even if appellees raised it later. *See McLean Contracting Co. v. Waterman Steamship Corp.*, 277 F.3d 477, 480 (4th Cir. 2002) ("Failure to identify a legal issue worthy of trial in the pretrial conference or pretrial order waives the party's right to have that issue tried.").

Even if appellees did not waive this issue, their belated arguments raised towards the end of trial are unavailing. First and foremost, the question is not whether, as appellees seem to argue, Dr. VanDenburgh or Dr. Brandt was the first to recognize bimatoprost's potential therapeutic value for eyelash hair growth. Appellants do not argue that the Brandt references expressly teach bimatoprost's intentional use to grow hair—that is, they do not argue inventorship. The relevant inquiry must be whether the Brandt references, which describe the methods, detailed results, statistical analysis and discussion of bimatoprost clinical trials, were solely Dr. VanDenburgh's work and hers alone. *In re Katz*, 687 F.2d at 455. On this, appellees' explanations strain reason.

First, Dr. VanDenburgh's testimony was at best equivocal as to whether she alone directed clinical trials and wrote internal reports. J.A. 508, 540-41. Second, while she was at least a co-author of one Brandt reference

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[12] Letter from Appellees, ECF No. 93 (attaching "excerpts from the closing argument transcript, Allergan and Duke's post-trial brief, and Allergan and Duke's post-trial findings of fact and conclusions of law" regarding this issue).

in dispute, along with two other Allergan scientists, Dr. VanDenburgh was not listed as a co-author at all in the other one. Brandt's May 2001 journal article includes one co-author, Dr. Sherwood, also unaffiliated with Allergan. The author line of the latter article describes it as being written "for the Bimatoprost Study Group 1 or 2," referring to a long list of study group members—a list in which Dr. VanDenburgh's name does not appear. J.A. 2413-14. The fact that a reference does not list any co-inventors as authors, or that it lists other authors, is certainly not dispositive in itself. However, in this case, whether Dr. VanDenburgh supervised the logistics of the clinical trial on her own or not, appellees have not produced evidence that shows she was responsible for directing the production of either article's content, which includes the design, trial, and analysis of results. There is no evidence, therefore, that appellees' explanation of the Brandt references is in any way consistent with the content of the articles and the nature of the publications. *In re Katz*, 687 F.2d at 455.

Since appellees have produced no evidence—unsurprising given their belated recourse to this argument—and provided no supported explanation demonstrating that the Brandt references were in fact printed publications authored by Dr. VanDenburgh for the purposes of § 102(a), we see no reason to remand to make further findings on this issue. The question of whether a reference is a work of others for the purposes of § 102(a) is, like that of inventorship, a question of law based on underlying facts. *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998). Even if appellees had not waived their arguments on this point, the evidence appellees presented at trial could not support the legal conclusion that the Brandt references represented Dr. VanDenburgh's own work. *See Soverain Software LLC v. Newegg Inc.*, 705 F.3d 1333, 1337 (Fed. Cir. 2013) *amended on reh'g*, 728 F.3d 1332 (Fed. Cir. 2013) and *cert.*

denied, 134 S. Ct. 910 (2014) (declining to remand for further factual findings on obviousness where there was no material factual dispute and the legal conclusion was apparent). Accordingly, we hold that the Brandt references are prior art to the '404 patent.

2. Invalidity

The district court's findings on the obviousness of the '404 patent were limited to reiterating that the May and June 2001 Brandt references were not prior art (as a consequence of its finding on the mid-2000 invention date of the '404 patent) and that the '404 patent was not obvious in light of Johnstone alone. *Allergan*, 2013 WL 286251, at *10. The district court did make findings regarding inherent anticipation in light of the two earlier Brandt references. Paralleling its reasoning on inherent anticipation by the '819 patent, as discussed above in section III.A.1.b, the district court found that the disclosure of 48.4% incidence of eyelash growth did not inherently anticipate. *Id*. at *8. While we need not reach the question of whether the district court's inference represents clear error, we do note that the Brandt references disclose a substantial rate of eyelash hair growth as a side effect of using bimatoprost in eyedrops.

Johnstone details at length how eyedrops containing latanoprost (marketed as the glaucoma drug Xalatan®) promote the eyelash hair growth through the mechanism of fluid containing latanoprost making topical contact with the eyelid. Johnstone at 22 ll. 28-35. Johnstone also discloses the topical application of latanoprost to treat hair loss. In light of the Brandt reference's disclosure of bimatoprost's effect in growing eyelash hair, a person of ordinary skill in the art would have had substantial motivation to follow Johnstone and use topical application of bimatoprost to grow eyelash hair.

Likewise, the Brandt references provided a reasonable expectation of success for the topical application of bima-

toprost. Clinical trials showed that nearly 50% of patients using bimatoprost in eyedrop form were experiencing eyelash hair growth. Johnstone additionally taught that fluid contacting the eyelid from eyedrops was the likely mechanism of hair growth. Appellees' only remaining argument for nonobviousness in light of the Brandt references is the secondary consideration of commercial success, which is unavailing on its own.

Given the overwhelming weight of evidence, remand is unnecessary "as here, the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors." *Soverain*, 705 F.3d at 1337 (citing *KSR*, 550 U.S. at 427). Accordingly, we reverse the district court's finding that the '404 patent is not invalid for reasons of obviousness.

CONCLUSION

For the foregoing reasons, we reverse the district court's invalidity findings on the asserted claims of both the '029 and '404 patents, and we vacate the court's injunction accordingly.[13]

REVERSED AND VACATED

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[13] Because we reverse the court's invalidity finding on both asserted patents on the grounds of obviousness and thus vacate the court's injunction, we need not reach appellants' arguments regarding insufficient written description for the asserted claims of the '029 patent and inadequate enablement of claim 14 of the '404 patent, as well as the question of whether the court abused its discretion in granting a permanent injunction.

United States Court of Appeals for the Federal Circuit

ALLERGAN, INC., AND DUKE UNIVERSITY,
Plaintiffs-Appellees,

v.

APOTEX INC., APOTEX CORP., SANDOZ, INC., AND HI-TECH PHARMACAL CO., INC.,
Defendants-Appellants.

2013-1245, -1246, -1247

Appeals from the United States District Court for the Middle District of North Carolina in Nos. 10-CV-0681, 11-CV-0298, and 11-CV-0650, Judge Catherine C. Eagles.

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ALLERGAN, INC., AND DUKE UNIVERSITY,
Plaintiffs-Appellees,

v.

WATSON PHARMACEUTICALS, INC., now known as Actavis, Inc., WATSON LABORATORIES, INC., AND WATSON PHARMA, INC.,
Defendants-Appellants.

2013-1249

Appeals from the United States District Court for the Middle District of North Carolina in No. 12-CV-0321, Judge Catherine C. Eagles.

CHEN, *Circuit Judge*, dissenting-in-part.

I join the majority opinion except for Part II.A.2, which reverses the district court's conclusion that Appellants failed to meet their burden of proving that the prior art rendered the '029 patent obvious by Johnstone, either alone or in combination with the '819 patent. In my view, Johnstone's teachings are simply too vague and equivocal to justify invalidating the patent. Therefore, I respectfully dissent.

To begin with, issued patents enjoy a presumption of validity, which can only be rebutted by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship,* 131 S. Ct. 2238, 2245–46 (2011). A party challenging a patent's validity must do so with "evidence which produces in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions are highly probable." *Buildex Inc. v. Kason Indus., Inc.*, 849 F.2d 1461, 1463 (Fed. Cir. 1988) (citing *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984)). This is not a burden that is easily satisfied.

Moreover, the majority relies heavily on Johnstone alone, but the Patent Office specifically considered that reference during the prosecution of the '029 patent and came to the same conclusion that the fact-finder did below: Johnstone does not render the claims obvious. As a reviewing court, we should be particularly careful before overturning the verdict under these circumstances. *See Tokai Corp. v. Easton Enterprises, Inc.*, 632 F.3d 1358, 1367 (Fed. Cir. 2011) (explaining that the burden of proof

to invalidate a patent claim is more difficult to meet when the challenge is based on the same prior art considered by the Patent Office during examination).

The majority is correct that Johnstone contemplates a large class of prostaglandins—the 17-phenyl PGF2 analog compounds—citing latanoprost in particular, for treating hair loss. But that reference does not teach or sufficiently suggest using a prostaglandin with a saturated (i.e., single) C_5-C_6 bond on the alpha chain, as claimed in the '029 patent. Instead, Johnstone serves up a menu of seemingly unlimited possibilities. For example, when it comes to the alpha chain, Johnstone states that the good ones are those characterized by "the presence or lack of various modifications of the alpha chain." J.A. 2293. Then, for the omega chain, Johnstone again states that preferred prostaglandins are those characterized by the "presence or lack of modifications to their omega chain." *Id.* Such a broad, generic disclosure would appear to cover almost any conceivable prostaglandin. And among a variety of other possible modifications for the chains, Johnstone vaguely states that the alpha chain "could preferably be a C_6-C_{10} chain which can be either saturated or unsaturated, having one or more double bonds, and allenes or a triple bond." J.A. 2293. This lone sentence does not provide a sufficient blaze mark for using a saturated C_5-C_6 bond. For the same reason that I agree with the majority that Johnstone does not anticipate the claimed compounds—it does not "clearly and unequivocally" disclose a compound with a saturated C_5-C_6 bond—I would find that it does not suggest one either. The specification contains no other language or examples of saturated alpha chains and certainly no references to saturating the specific bond at issue. The dozens of figures and summary of the invention only depict an unsaturated (i.e., double) C_5-C_6 bond, and Johnstone's claims cover only compounds with this bond. The steady and persistent message from the entirety of Johnstone's

teachings is clear: when it comes to the C_5-C_6 bond, keep it unsaturated.

Also, as the majority recognizes, the patentee amended the claims during prosecution to add a proviso carving out the Johnstone compounds, which resulted in a notice of allowance. The notice of allowance even pointed out that the amended claims were not obvious over Johnstone:

> The prior art teaches the use of prostaglandins for treating hair loss (see for example, WO 98/33497 [Johnstone]). However, the prior art lacks motivation to modify the prostaglandins taught therein in order to obtain the presently claimed prostaglandins, and thus, does not teach or suggest the presently claimed invention.

J.A. 5564. In light of the particularly heavy burden to show obviousness over a reference disclosed during prosecution and discussed by the examiner, Appellants have not shown that Johnstone now somehow teaches or suggests the very structural feature that the patentee claimed to distinguish the Johnstone compounds.

Nothing in the record compels a different result. Allergan's expert, Dr. MacDonald, testified that a person of ordinary skill would not have saturated Johnstone's C_5-C_6 double bond because "[i]t was considered to be a very important parameter in binding to the FP receptor." J.A. 1773. Prostaglandins bind to receptors on the surface of cells, and that binding creates a signal to the cell to change its properties or functions. At the time of invention, it was well-understood that identifying which receptors a prostaglandin can bind to is key to designing a drug that affects the cells. *See* J.A. 23 ("Studying receptors is central to pharmacology—the science of drug therapeutics—because knowing what receptors are associated with a biological effect aids in designing a drug to [bind to] those receptors and produce or inhibit that effect."). And,

at that time, the state of the art suggested that saturating the C_5-C_6 bond in Johnstone's compounds would have destroyed the critical binding property of the compounds. *Id.* at 30 ("Before [the inventor of the '029 patent] discover[ed] that saturated prostaglandin F analogs could bind, this double bond was thought vital for FP-receptor binding."). The '029 patent's compounds have saturated C_5-C_6 bonds but do, in fact, bind to the FP-receptor (contrary to popular belief at the time), which further suggests nonobviousness. *See DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). The majority finds no clear error in the district court's acceptance of this undisputed fact for purposes of anticipation. *See* Majority Op. at 10. I would also find that the district court correctly concluded that it would not have been obvious to a person of ordinary skill at the time of invention to change the unsaturated C_5-C_6 bond in Johnstone's compounds to a saturated bond. *See DePuy*, 567 F.3d at 1326 (suggesting nonobviousness "if the prior art indicated that the invention would not have worked for its intended purpose or otherwise taught away from the invention"); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (holding prior art supplied no motivation to modify compound to include claimed structural features because no reasonable expectation of success).

This is not a situation in which there are a finite number of identified, predictable solutions. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). Rather, the single sentence in Johnstone actually proposes hundreds of thousands, or even millions, of variations on the alpha

chain.[1] *Cf. Eli Lilly*, 471 F.3d at 1376 (prior art reference that disclosed millions of compounds did not spell out "a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited class"). The compound in Johnstone could have a saturated bond at any position on the alpha chain, an unsaturated bond at any position, a triple bond at any position, or even a combination of any of these bonds. As a result, a person of ordinary skill in the art was not faced with a "small or easily traversed" number of options based on Johnstone. *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) ("[A]n invention would not have been obvious to try when the inventor would have had to try all possibilities in a field unreduced by direction of the prior art."). In this instance, covering everything effectively tells us nothing. *See Bayer*, 575 F.3d at 1347 ("When what would have been obvious to try would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful an invention would not have been obvious.") (internal quotations omitted).

The majority further reasons that it would have been obvious to select the claimed compounds because they, like Johnstone's compounds, also "exhibit high pharmacological activity and no or very small side effects." Majority Op. at 20. But the fact that we now know that the

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[1] To the extent that the majority maintains that Johnstone does not cover thousands of possibilities, Majority Op. at 22, I respectfully disagree. True, Johnstone reaches specific classes of compounds, but Johnstone's suggested modifications, which the majority relies on, cover many more variations.

claimed compounds contain highly desirable properties should not compel us to conclude that this would have been obvious at the time of invention, especially when there is no expert testimony or other evidence in the record supporting the notion that it would be obvious to treat hair loss using any prostaglandin that exhibits "high pharmacological activity." *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1088 (Fed. Cir. 2008) ("Only with hindsight knowledge that the dextrorotatory enantiomer has highly desirable properties, can Apotex argue that it would have been obvious to select this particular racemate and undertake its arduous separation.").

I also depart from the majority's combination of Johnstone with the '819 patent. Following the Appellants' argument, the majority links Johnstone's methods of treating hair loss and the '819 patent's methods of treating glaucoma by looking to the vasodilation properties shared by the compounds in those references. Majority Op. at 19–20. I find Johnstone's discussion of vasodilation too ambiguous to amount to a clear motivation to combine.

For example, Johnstone states that "PGF2 alpha analogs can cause a vasodilation effect and through that mechanism *may* provide enhanced perfusion to the region of the hair bulb and thus stimulate increased trophic activity in the hair follicles." J.A. 2291–92 (emphasis added). That Johnstone frames his vasodilation theory in somewhat uncertain terms ("may") is not surprising since he later acknowledges that his representative prostaglandin derivative, latanoprost, "was specifically tailored to eliminate . . . vasodilation." *Id.* at 2290. Ultimately, Johnstone surmises that there are "several possible mechanisms that may individually or in concert explain the altered growth pattern of hair follicles observed in the current clinical study." *Id.* at 2291. This level of uncertainty in Johnstone cannot then establish motivation to combine with the '708 patent and then with '819 patent.

Unlike the Brandt references, which suggested that bimatoprost could be used to grow hair, the '708 and '819 patents have nothing to do with hair growth. These patents concern treatment methods for glaucoma. Appellants have not established by clear and convincing evidence that a person of ordinary skill in the art would look to these references for solutions in the hair growth field. This is especially true when the correlation between vasodilation and hair growth—the alleged link between Johnstone and the '819 patent—is so speculative. *See Star Scientific, Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011) (reference's discussion of what "might" or "may" or "seems" to lead to nitrite and TSNA production does not suggest obviousness).

Appellants further assert that one of ordinary skill in the art would use the compounds disclosed in the '819 patent with Johnstone's method of stimulating hair growth because Johnstone refers to the '708 patent, which is the parent of the '819 patent.

But Johnstone's link to the '819 patent via the '708 patent is tenuous at best. Johnstone describes "preferred derivatives" for hair growth as those compounds lacking a phenyl ring structure in their omega chains, such as those described in the '708 patent. J.A. 2298. Any motivation to combine Johnstone with the compounds of the '819 patent via the '708 patent is then confined to those compounds lacking a phenyl ring structure. The '819 patent, however, teaches bimatoprost, which has a phenyl ring structure in its omega chain. Thus, as the majority concedes, "the list of compounds expressly disclosed [in Johnstone] as being vasodilatory in the '708 patent exclude the 17-phenyl PGF analogs that the '819 patent discloses." Majority Op. at 20 n.8. Consequently, Johnstone's reference to the '708 patent simply does not amount to a motivation to combine Johnstone with the '819 patent.

It is undisputed that the field of hair growth is "unpredictable and mysterious." *See* J.A. 38. The majority errs in minimizing this unpredictability. Majority Op. at 21 ("But, it does not matter whether hair growth is generally an unpredictable endeavor . . . ."). Our case law makes plain: unpredictability is a factor. *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("To the extent an art is unpredictable, as the chemical arts often are . . . potential solutions are less likely to be genuinely predictable."). In light of our case law and the unpredictability of hair growth, Appellants have not satisfied their burden of showing clear and convincing evidence of obviousness.

Accordingly, looking at the evidence of obviousness as a whole, I would find that the district court did not clearly err in holding the asserted claims of the '029 patent nonobvious. For these reasons, I respectfully dissent.